REMARKS

The Applicant acknowledges that a number of the previously maintained rejections have been withdrawn. The rejections of claims 1 and 14-18 as anticipated by *Melton et al.* and of claims 5-6 and 8 as obvious over *Logan et al.* in combination with *Alexander et al.* and *Mattson et al.* are maintained. In addition, the Examiner has newly rejected the subject matter of present claims 1 and 14-18 as obvious over *Melton et al.* in combination with *Alexander et al.* and *Mattson et al.* These rejections are respectfully traversed in light of the indicated amendments and remarks below, and reconsideration is requested.

The pending claims have been amended as indicated to replace references to "TGF-β" with "TGF-β1, TGF-β2 and/or TGF-β3." Applicant submits that this amendment is supported throughout the specification, e.g., at p. 2, lines 17-18. Thus, no new matter has been added.

Applicant's amendment of certain rejected claims is not to be construed as an admission that the Examiner's rejections were proper. The Applicant continues to believe that the rejected claims are described in and enabled by the specification, and are neither anticipated by nor obvious in view of the cited references, as previously argued. The rejected claims have been amended for the sole purpose of advancing the case to allowance. The Applicant reserves the right to file a continuing application to continue the prosecution of the rejected claims.

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Rejection of claims 1 and 14-18 as either anticipated by or obvious over *Melton et al.*

Melton et al. discloses a method for inducing neuronal differentiation and preventing the death or degeneration of neuronal cells by antagonizing a growth factor of the TGF-β family. As defined in *Melton et al.* on page 6, lines 27-31, the term TGF-β

> "*denotes a family of structurally related paracrine polypeptides found ubiquitously in vertebrates, and prototypic of a large family of metazoan growth, differentiation, and morphogenesis factors (see, for review, Massague et al. (1990) Ann Rev Cell Biol 6:597-641; and Sporn et al. (1992) J Cell Biol 119:1017-1021).*"

The cited article of Massague, 1990, a copy of which is enclosed (Exhibit I), reveals immediately that the definition of TGF-β provided in *Melton et al.* relates not to the "real" TGF-βs, only five of which are known to date (TGF-β1 to TGF-β5), but to the whole TGF-β family (also called superfamily), an extremely large and biochemically heterogeneous group of TGF-β related factors with a variety of functions, see e.g. the cited article of *Massague et al.* on page 598, second paragraph:

> "*Besides being multifunctional, TGF-β represents a large family of factors with diverse activities. The concept that TGF-β is prototypic of a superfamily of growth, differentiation, and morphogenesis factors became clear in 1987 (Massague 1987, Sporn et al. 1987) following the rich harvest that yielded the*

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> *inhibins, activins, Müllerian inhibiting substance, decapentaplegic product, and TGF-β2. One after another, these factors proved to be structurally related to TGF-β. This family now includes embryogenic morphogens, regulators of endocrine function, and broad-spectrum as well as specialized regulators of cell proliferation and differentiation.*"

This broad TGF-β definition of *Melton et al.* becomes absolutely clear also from said document itself because an especially preferred growth factor of the Melton et al., invention is activin, a substance belonging to the TGF-β (super)family but *not* to the subgroup consisting of TGF-β1 to TGF-β5, see *Melton et al.* page 5, line 27 to 28:

> "*As described below, activin is strongly implicated as the TGF-β type growth factor that inhibits neuronal differentiation.*"

However, although the disclosure of *Melton et al.* is very broad and mentions the TGF-β (super)family in general, this document fails to provide an enabling disclosure of the specifically claimed methods of the instant invention for inducing and maintaining neuronal cells with, *e.g.*, antagonists of TGF-β1 to TGF-β5. It should be mentioned in this context that the TGF-β (super)family of growth factors as defined in *Melton et al.* now includes more than 25 different members which are structurally related to each other, but show a multitude of biological functions and elicit their different effects by binding to various unique cell surface receptors (see, *e.g.*, Table 1 (The transforming growth factor β (TGF-β) family and representative

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activities) of Massague, 1998, a copy of which is enclosed (Exhibit II)).

Referring to the disclosure content of *Melton et al.*, it becomes immediately evident that these authors only examined signal transduction pathways of those TGF-β (super)family members that bind to specific activin receptors, see e.g. p. 5, lines 18 to 24:

> "*As described in the examples below, our results indicate that activin, or any other member of the TGF-β family that interacts with the truncated activin receptor, can inhibit neural induction, as these TGF-β signals instruct cells towards non-neuronal facts such as epidermal, mesodermal or endodermal fate. Inhibition of signal transduction by a TGF-β-type receptor, by either the truncated activin receptor, follistatin, or inhibin, induced cells of the intact animal cap to switch to a neuronal fate in the absence of any detectable mesoderm.*";

further, p. 21, lines 9 to 16:

> "*Example 1: Inhibition of activin signalling by a truncated activin receptor induces neural structures in vivo.*
>
> *To demonstrate the assertion that neuralization represents a default state requiring the inhibition of endogenous activin molecules, the ability of a dominant negative activin receptor to induce neuralization ectopically in embryos was assigned. A truncated version of XAR1 was constructed to contain the entire extracellular and transmembrane domains but which lacks nearly all of the cytoplasmic domain, including the serine/threonine kinase.*"

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All other examples of *Melton et al.* refer also to either the activin receptor XAR1 or the specific activin antagonist follistatin.

Furthermore, it is important to note that the examined activin receptor XAR1 is a Xenopus type II activin receptor better known as ActRIIB; see, *e.g.*, the article of Chang et al., 1997, a copy of which is enclosed (Exhibit III), lines 2 to 4 of the SUMMARY:

> "*Disruption of signalling by a truncated type II activin receptor, XActRIIB (previously called XAR1) blocks mesoderm induction and promotes neuralization in Xenopus embryos.*"

Moreover, the same article states clearly that, in contrast to activin, TGF-β does not bind to type II activin receptors such as XAR1, see page 827, end of second column:

> "*Although activin and TGF-β display no apparent binding of functional interactions with each others receptors, it appears that there may be significant sharing of receptors between activin and BMPs.*"

This statement is also confirmed by the already cited Massague, 1998; see page 758, second paragraph:

> "*In vertebrates, the type II receptor subfamily includes TβR, BMPR-II and AMHR, which selectively bind TGF-β, BMPs, and MIS, respectively. ActR-II and -IIB bind activins when expressed alone or in concert with activin type I receptors. However, ActR-II and -IIB can bind BMPs 2, 4, and 7 and GDF-5 in concert with BMP type I receptors.*"

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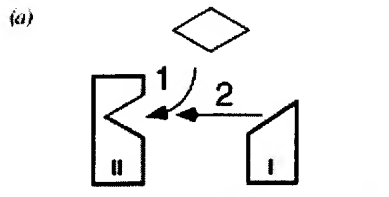
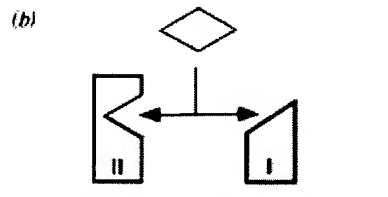
Accordingly, figure 3 on page 761 also shows that the type II receptors for activin are ActR-II and ActR-IIB, whereas TGF-β binds to TβRII:



Ligand	Receptor II	Receptor I
TGF-β	TβR-II	TβR-I
Activin	ActR-II ActR-IIB	ActR-IB ActR-I
MIS	AMHR	ActR-I?



Ligand	Receptor II	Receptor I
BMP2 BMP7 GDF5	BMPR-II ActR-II ActR-IIB	BMPR-IA BMPR-IB ActR-I
Dpp	Punt	Tkv Sax

Figure 3 Two modes of ligand binding: (*a*) sequential binding, (*b*) cooperative binding. The ligands that bind according to each mode are listed together with the type I and II receptor combinations that they recognize. TGF, transforming growth factor; BMP, bone morphogenetic protein; GDF, growth and differentiation factor; MIS, Müllerian inhibiting substance.

In summary, *Melton et al.* indeed succeeds in showing that those (and only those) TGF-β (super)family members that bind to activin type II receptors (and particularly to ActRIIB) have neurotrophic effects (*e.g.*, activin: see examples of *Melton et al.*). However, *Melton et al.* is completely silent about the specific TGF-β (super)family members TGF-β1, -β2 and -β3 referred to in the instant claims, since these proteins bind to other receptor types than activin and, evidently, mediate different signals and, therefore, cause different effects.

Additionally, *Melton et al.* obviously fails to provide an enabling disclosure of a method for inducing neuronal differentiation and preventing the death or degeneration of

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neuronal cells by antagonizing specifically TGF-β1, TGF-β2 or TGF-β3. As shown above, these three proteins do not bind to activin type receptors which interact only with the TGF-β proteins enablingly disclosed in *Melton et al.* (such as activin).

Therefore, Melton et al., cannot anticipate the claimed invention and the rejection under section 102(b) has been overcome. Nor are the indicated claims obvious over Melton et al., in combination with Alexander et al., and Mattson et al., as neither of these references can supply the features missing in Melton et al.

Rejection of claims 5-6 and 8 as obvious over *Logan et al.*

Referring to section 5. of the Official Action, the Examiner holds the view that the subject matter of claims 5 to 6 and 8 is obvious over *Logan et al.* in combination with *Alexander et al.* and *Mattson et al.*

Regeneration in the CNS is impeded by at least three mechanisms: (i) the persistence of growth inhibitory myelin proteins in the distal stump, (ii) scar formation at the lesion site, and (iii) cell death of the neuronal perikarya.

The present application discloses the protection of predamaged or injured nerve cells (neurons) by antagonizing the TGF-β mediated execution of neurons. This invention is extremely important for the treatment of diseases which are characterized by the gradual degeneration and death of neurons. TGF-β mediated execution of neurons occurs whenever nerve cells are seriously damaged, for example in ischemic spinal cord injuries. More specific examples are neurodegenerative diseases such as ALS,

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Alzheimer's or Parkinson's disease. In these later types of CNS diseases, scar formation is only a minor issue.

In contrast thereto, *Logan et al.* describes the prevention of scar formation by antagonizing a second and obviously different effect of TGF-β proteins, namely the promotion of scarring by extracellular matrix material production. Mediated by TGF-βs, the human body starts building a collagenous scar a short time after seizure of nerve cords or axons. This scar is formed from connective tissue such as, e.g., glial cells (and not from neurons) and acts as a rigid physical barrier which blocks the path of rejoining or reconnecting nerve cords. It does not cause neuronal execution at all. Nerve fibers cannot regenerate across scar tissue. The growing neurons and nerve fibers are simply not able to reach and re-contact their counterparts at the other side of the barrier and, therefore, fail to transduce the electric signals. This is clarified on page 8, lines 20 to 23 of *Logan et al.*:

> "*Accordingly, the present invention provides a method for preventing, suppressing or treating CNS pathologies characterized by a deleterious accumulation of extracellular matrix in a tissue.*",

and also on page 7, lines 6 to 10:

> "*The results suggest that a reduction of the dense permanent scar that is deposited at the site of injury, and which blocks the path of regenerating neurons, is one step towards achieving functional reconnection of damaged neural pathways to their target organs.*"

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and most apparently from the wording of claim 1 of *Logan et al.*:

> "*A method for preventing, suppressing or treating a CNS pathology characterized by a deleterious accumulation of extracellular matrix in a tissue of the CNS, comprising contacting said tissue with an agent that inhibits the extracellular producing activity of TGF-β.*"

A major feature of this claim is the prevention of accumulation of the extracellular matrix, whereby the building of scars is inhibited (cf. *Logan et al.* page 1, line 30: "The mature scar, with its dense fibrous connective tissue bordered by an astrocytic glia limitans, is a physical barrier to axonal growth."). Herein it is also described that the scar is formed from connective tissue and not from neurons.

Therefore, since *Logan et al.* merely teaches that TGF-β antagonists may prevent scar formation, wherein said scars build a barrier for the growth of nerves, but does not describe any impact of the TGF-β antagonists directly onto the injured nerve itself, the disclosure content of *Logan et al.* is not expected to direct a person skilled in the art to the subject matter of the present application without requiring any inventive effort.

In particular, a method of treating scar formation, as in Logan et al., which is a *slow process*, would not suggest combining a composition for such treatment with a composition for treating blood clots as instantly claimed in claims 5-6 and 8.

The Examiner states at p. 5 of the Office Action that "Alexander et al. teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral

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hemorrhage." However, nothing in the teachings of Logan et al. suggests or implies any sense of urgency, any sense that the patients to be treated in Logan et al. are "at risk for cerebral hemorrhage." This concept is *imported* by the Examiner *with hindsight reasoning from the Applicant's claims*. The Examiner must find that the prior art combination suggests the claimed invention, not the other way around!

Thus, there is no motivation in either Logan et al. or Alexander et al. to combine a composition for decreasing scar formation with a composition for treating blood clots, *which have nothing to do with scar formation*.

Further, *Mattson et al.* provides nothing that is lacking in a combination of Logan et al. with Alexander et al. and, thus, the rejection is overcome.

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CONCLUSION

In view of the remarks presented herein, reconsideration and withdrawal of the rejections by the Examiner and allowance of the application with the pending claims are respectfully requested.

The Examiner is also encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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